**DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/13/2009 has been entered.

Applicant's arguments filed 11/13/2009 have been fully considered. Claims 1-21, 43-46, 48-65 are pending and under consideration. Claims 22-42, 47 have been canceled.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejection of claims **1-8, 13, 17-18, 43, 48, 60, 62** under 35 U.S.C. 102(e) as being anticipated by Hawley et al, (US 2006/0242722 A1) for the reasons of record of the previous office action mailed 10/03/08 is withdrawn in view of the declaration filed on 11/13/2009.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1-18, 43-46, 48-65 remain** rejected under 35 U.S.C. 103(a) as being unpatentable over **Lai et al,** (Science, 295: 1089-1092, February 2002) in view of **Straham et al,** (Frontiers in Bioscience, 1, e34-41, 1996).

Applicants argue at the time of filing there were well recognized differences in a-Gal epitope expression between mice and pigs, based on which one of ordinary skill in the art would have lacked any expectation that results obtained in mice could be applied to pigs. Furthermore, the art was filled with statements supporting that a person of ordinary skill in the art would not believe that any aGal-negative pigs would be viable. The Applicant supported these assertions with references including:

• Tanemura and Galili (2000) Transplantation Proceedings. 32:843), which showed that pig organs express between 10 and 500 times the a-Gal levels of mice organs and that these raise the concern that "pigs may not be able to develop in the absence of a-gal epitopes";

• Galili, U. ((2001) Biochimie 83:557-563), which notes that the abundant expression of a-Gal in pigs as compared to all other animals" throws doubt onto whether a homozygous aGT-negative animal would survive;
• Ayares et al. ((2001) Graft 4:80-85), which notes "[since] Gal epitope expression in pig organs is up to 500-fold higher than in mouse organs, there is the possibility that aGT activity is more crucial to the pig";
Sharma et al. ((2003) Transplantation 75:430-436), which notes "it is possible that GT(-/-) pigs may not be viable because the GT gene is essential for embryonic development";

• Porter & Dallman ((1997) Transplantation 64:1227-1235), which notes "[a]lthough [aGT-negative mice] develop and remain fairly normal, the possibility exists that deletion of this enzyme could have more severe consequences in other animals;" and
• Denning et al. ((2001) Nature Biotech 19:559-562), which showed actual lack of success in producing viable aGT sheep when attempts were made to produce such animals.

These arguments are not persuasive because while all the above references raise the concern that the abundantly expressed α-gal epitope may have some biological roles in pig development, such as in cell-cell interaction however, Lai teaches a-1,3-alactosyltransferase–null mice have already been produced, and it is not anticipated that this genetic modification will be lethal in the null animals. Lai suggests that a-1,3-galactosyltransferase–null pigs will not only eliminate hyperacute rejection (p 1092, 1st column, last paragraph). Strahan et al teach the (1,3) galactosyltransferase epitope is the major target for human anti-pig natural antibodies leading to the events that precipitate the hyperacute rejection; teaches attempts are being made to produce transgenic pigs with reduced levels of expression of the α(1,3) galactosyltransferase epitope and as such, Strahan et al provide sufficient motivation for one of ordinary skill in the art to breed the heterozygous α(1,3) galactosyltransferase pigs produced by Lai in order to obtain homozygous pigs with no expression of the (1,3) galactosyltransferase.

Furthermore, **Clark et al** (Nature Reviews, Genetics, 4 : 825-833, 2003) note there are several endogenous genes, such as the prion protein (*PrP*) and α(1,3)galactosyltransferase genes, the deletion of which is predicted to yield unique, useful phenotypes in livestock (p 828, 1st column, 1st paragraph). In addition, Clark notes to achieve the phenotype both alleles must be deleted. At present, it is only possible to target one gene *in vitro* and so homozygous nulls must be generated by crossing independently generated male and female clones, or by retargeting and recloning (p 828, last column, and 1st paragraph). Recently, the generation of piglets with both copies of the α(1,3)galactosyltransferase gene knocked out has been described referring

to the applicant's transgenic pig but, unexpectedly, homozygous knockout pig fibroblasts generated by

the Straham research group express low levels of the gal antigen referring to Straham pig [Sharma et al. ((2003) Transplantation 75:430-436)], (p 828, last column, 1st paragraph). Therefore, in contrast to Applicant's assertion the Sharma et al. reference notes "it is possible that GT(-/-) pigs may be viable.

Applicants argue a person of ordinary skill in the art would ignore the well recognized differences between pigs and mice and the multiple references that noted that pigs, in contrast to mice, were expected to lack viability. The Applicant has provided more than five separate references, predating the present invention that articulates the expected lack of viability of the aGal-negative pigs. The Applicant has even provided evidence that, when such a mutation was attempted in another ungulate, it was not successful. The debate on this matter supports that a person of ordinary skill in the art at the relevant time would have lacked any reasonable expectation that such animals would be viable. The Applicant has provided substantial evidence to show that one of ordinary skill would not have expected any combination of the references cited by the Examiner to produce viable pigs lacking functional expression of aGT, as presently claimed. Only with the Applicant's present invention did the hope for viable pigs lacking functional a-Gal become a reality. The Applicant respectfully requests withdrawal of this rejection.

These arguments are not persuasive because while all the above references raise the concern that the abundantly expressed a-gal epitope may have some biological roles in pig development, such as in cell-cell interaction however, Lai teaches a-1,3-alactosyltransferase–null mice have already been produced, and it is not anticipated that this genetic modification will be lethal in the null animals. Lai suggests that a-1,3-galactosyltransferase–null pigs will not only

eliminate hyperacute rejection (p 1092, 1st column, last paragraph). Strahan et al teach the (1,3) galactosyltransferase epitope is the major target for human anti-pig natural antibodies leading to the events that precipitate the hyperacute rejection; teaches attempts are being made to produce transgenic pigs with reduced levels of expression of the α(1,3) galactosyltransferase epitope and as such, Strahan et al provide sufficient motivation for one of ordinary skill in the art to breed the heterozygous α(1,3) galactosyltransferase pigs produced by Lai in order to obtain homozygous pigs with no expression of the α(1,3) galactosyltransferase. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Lai teaches the production of a-1,3-galactosyltransferase heterozygotes and also teaches the next step will be to create α-1,3-galactosyltransferase–null (homozygous knockout) pigs, either by breeding to a heterozygous male produced by nuclear transfer or by sequential nuclear transfer modification of cell lines produced from the four female pigs produced by Lai (p 1092, 1st column, last paragraph). Because α-1,3-alactosyltransferase–null mice have already been produced, it is not anticipated that this genetic modification will be lethal in the null animals. Lai suggests that a-1,3-galactosyltransferase–null pigs will not only eliminate hyperacute rejection but also ameliorate later rejection processes, and (in conjunction with clinically relevant immunosuppressive therapy) will permit long-term survival of transplanted porcine organs (p 1092, 1st column, last paragraph). At a minimum, the availability of galactosyltransferase-null pigs will allow a clearer evaluation of approaches currently in development aimed at overcoming

potential delayed and chronic rejection mechanisms in porcine xenotransplantation (p 1092, 1st column, last paragraph). Strahan et al teach the α(1,3) galactosyltransferase epitope is the major target for human anti-pig natural antibodies leading to the events that precipitate the hyperacute rejection; teaches attempts are being made to produce transgenic pigs with reduced levels of expression of the (1,3) galactosyltransferase epitope and as such, Strahan et al provide sufficient motivation for one of ordinary skill in the art to breed the heterozygous α(1,3) galactosyltransferase pigs produced by Lai in order to obtain homozygous pigs with no expression of the α(1,3) galactosyltransferase.

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***Allowable Subject Matter***

Claims **19-21** are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Conclusion***

**No claim is allowed.**

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful,

the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
Primary Examiner, Art Unit 1632